Preface

This document is the first revision of the Food and Drug Administration's 1982 "Redbook I" (*Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food*). The revised "Redbook II" is intended 1) to provide guidance regarding criteria used for safety assessment of direct food additives and color additives used in food and 2) to assist petitioners in developing and submitting for Agency review data for the safety assessment sections of petitions for these food additives under Section 21 of the Code of Federal Regulations (CFR). While the guidelines in this document do not preclude the petitioner from demonstrating safety by using other types of data, a submission conforming to the recommended scheme of toxicity testing would normally provide sufficient scientific information to assess safety.

In 1982, FDA and the Center for Food Safety and Applied Nutrition (CFSAN, then the Bureau of Foods) first published the "Redbook I" to describe the criteria the Agency employed for assessing the safety of direct food additives and color additives used in food. In revising "Redbook I" the Agency is taking into account developments in toxicity testing since 1982 and comments received from the scientific community and public concerning the 1982 "Redbook I." As with the 1982 "Redbook I," the tiered system for determining concern levels and minimum sets of toxicity tests for compounds assigned to each concern level are discussed in this document. In addition to conventional types of toxicity tests, new or significantly expanded sections include metabolism and pharmacokinetics, immunotoxicity, neurobehavioral toxicity, alternatives to whole animal testing, emerging issues in toxicity testing, pathology and statistical considerations, human studies, epidemiological studies, and carcinogenic risk assessment.

A major objective of the 1982 "Redbook I" was to make public the Agency's policy of cyclic review of the safety of additives in food. Since that time, the concept of cyclic review was abandoned and a program entitled "Priority-Based Assessment of Food Additives (PAFA)" was established. The PAFA program maintains a database of administrative, chemical and toxicological information on "Everything Added to the Food in the United States" (EAFUS), including the "Generally Recognized as Safe" (GRAS) compounds and all CFR regulated direct food additives and color additives used in food. It is beyond the scope of this document to provide a comprehensive list of all types of information in PAFA, or to provide a complete description of the procedures now used to evaluate data prior to inclusion in the database. The listing of the compounds that are contained in the PAFA database are available through CFSAN's web site:

http://www.cfsan.fda.gov/~dms/eafus.html
http://www.cfsan.fda.gov/~dms/opa-indt.html

Redbook II should provide useful guidelines to the petitioner in developing the toxicological safety data and documentation section in petition submissions for direct food additives and color additives used in food. A petitioner may follow the guidelines and protocols in "Redbook II," or may choose to use alternative procedures. If a petitioner chooses to use alternative procedures, however, he/she should discuss the procedures informally with the Agency to prevent expenditure of money and effort on activities that may later be determined to be unacceptable to the FDA.